## REMARKS/ARGUMENTS

Claims 214 and 215 have been amended for greater clarity in accordance with the specification at *e.g.*, p. 28, line 14 and the Examiner's suggestions as discussed below. Other claims have not been amended. No amendment should be construed as any acquiescence in any ground of rejection. Lack of comment on any of the Examiner's remarks should not be construed as agreement therewith.

Finality of rejection

The previous response added new claims 210-217 but did not amend claims 56-58, 61, 63-66, 71-79, 81, 85, 86, 92-94, 97, 99, 164-191, 194-205, and 207-209. The present office action contains numerous new grounds of rejection against claims that have not been amended (pp. 15-32 of the office action). Applicant understands the Examiner's position to be that if it is proper to make a new rejection final against the newly added claims, then the same rejection can be applied to any other claim, notwithstanding that such claims have not been amended. However, MPEP § 706.07(a) provides:

> *a second or any subsequent action* on the merits in any application or patent undergoing reexamination proceedings *will not be made final if it includes a rejection, on newly cited art*, other than information submitted in an information disclosure statement filed under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p), *of any claim not amended by applicant or patent owner in spite of the fact that other claims may have been amended to require newly cited art.*

Because the present office action applies new grounds of rejection to non-amended claims, it is respectfully submitted that finality should be withdrawn.

Applicant responds to the Examiner's comments using the paragraph numbering.

¶5. The finality of a new grounds of rejection against claims 85 and 204 is submitted to be improper for the reasons identified above.

¶¶6-8. Applicant maintains its request to hold provisional obviousness-type double patenting rejections in abeyance. Further, MPEP § 804 provides that if "provisional" obviousness-type double patenting rejections in two applications are the only rejections remaining in those applications, the examiner should withdraw the rejection in the earlier filed application, thereby permitting that application to issue without need of a terminal disclaimer. The present application has an earlier filing date than the two cited applications. Accordingly, if the present application is allowed first, the provisional obviousness-type double patenting rejections should be withdrawn.

¶¶9-10. Claims 56-58, 61, 63-66, 71-79, 81, 86, 92-94, 97, 99, 164-191, 194-203, 205 and 207-209 stand rejected as allegedly obvious over Anderson in view of Becker and Schenk.

The Examiner alleges that it does not matter that Schenk discusses the 266 antibody only for purposes of an in vitro diagnostic because it would still have been obvious to administer the antibody for in vivo diagnosis or therapy because of the property of the 266 antibody of binding to Aβ without binding to APP. However, according to MPEP 2141, the fact that elements in combination do not merely perform the function that each element performs separately serves as evidence against obviousness.

The Examiner further alleges that an inherent inability of the 266 antibody to bind plaques is irrelevant to the proposed use of the antibody for in vivo diagnosis because such inability was not known at the filing date. However, the Examiner does not address applicant's explanation of the relevance of this information. To reiterate, before the artisan went to the trouble of producing a chimeric or humanized version of 266 for in vivo diagnosis, the artisan would almost certainly have tested the mouse antibody for its capacity to bind to plaques. The artisan would have observed at best inferior performance of the 266 antibody and would likely have proceeded no further.

The Examiner alleges that contrary to the views of many disinterested experts there was nothing surprising about the invention because the art was allegedly replete with immunotherapeutic approaches. However, the approach of McMichael, US 5,753,624 was not

an immunotherapeutic approach, but rather an approach of negative feedback but otherwise not known in detail with any certainty:

> One explanation for the mode of action of this invention may be that the amount of this protein administered is sufficient to trigger a negative feedback mechanism to the body such that production of additional amyloid beta protein, possibly through breakdown of normal neurofilaments, is inhibited. Under this theory, the low level of amyloid beta protein, or a derivative thereof, gives a signal to the body to correct the abnormal synthesis/degradation process. The body sensors are then adjusted to normal metabolic control of amyloid beta protein processing that allows the proper balance to reestablish itself, alleviating the abnormal processing. The immune system, as well as the endocrine and CNS control systems, could play an integral regulatory role in response to the low dose therapy, with the amyloid protein functioning through mechanisms that not only correct the molecular organization of the amyloid beta protein moieties, but clear the interfering amyloid molecular constructs.
>
> '624 patent, detailed description, third paragraph.

The other cited references, like Becker, provide no evidence that an immunotherapeutic effect could be effective in modifying Alzheimer's disease. St. George Hyslop, US 5, 986,054 (for which applicants request clarification where it has been previously cited in the record) briefly mentions immunotherapy against presenilins, which are different proteins than Aβ, and in any event presents no evidence to suggest immunotherapy would be effective even against presenilins. Solomon concludes (last paragraph) by discussing further research on expressing antibody fragments using gene therapy, an approach probably reflecting concern that antibodies per se would not cross the blood brain barrier. Bickel reinforces concerns that antibodies are usually unable to cross the blood brain barrier. Although Bickel also discusses catonization as a means of improving the ability of antibodies to cross the blood brain barrier, he acknowledges that this approach raises question of whether modified antibodies retain activity, or acquire immunogenicity or other toxicity (*see* p. 124). The concerns expressed by others following Bickel (*see, e.g.*, Sangram S. Sisodia, University of Chicago. Science News Online 156, 2 (July 10, 1999), (cited by the IDS filed July 19, 2007 as cite no. 839) and in fact later work from the same group as Bickel (Pardridge et al., J. Am. Soc. Exp. Neurotherapeutics, 2:3-14 (2005))

suggest that the blood brain barrier was perceived as a serious obstacle to using antibodies to treat Alzheimer's disease notwithstanding Bickel. ("The combination of so little effort in developing solutions to the BBB problem, and the minimal BBB transport of the majority of all potential CNS drugs, leads predictably to the present situation in neurotherapeutics, which is that there are few effective treatments for the majority of CNS disorders," *see* Abstract).

The Examiner next alleges that because prior art references are presumed operable for purposes of an anticipation rejection, they must be presumed predictable for purposes of an obviousness rejection. However, operability and predictability are not one and the same. Predictability of the art is only one of eight factors used in a *Wands* analysis of enablement. Furthermore, the predictability at issue is not that of the reference but that of the claimed invention viewed in light of the reference.

The Examiner next alleges it was a well-known matter to sequence a sample of antibody at the protein level by Edman degradation to determine its amino acid sequence, deduce its cDNA sequence, and use the cDNA to make a humanized antibody. Applicant attaches an additional declaration by Dr. John Anderson from related co-pending application, US Application No. 10/923,471 on the difficulties of sequencing an antibody at the protein level. Dr. Anderson is an experienced scientist, who has used amino acid sequencing in his own work, and is familiar with the developments of amino acid sequencing over his career. Dr. Anderson explains the nature of Edman degradation amino acid sequencing, its primary use in determining short peptide sequences, and the difficulties that would be encountered if the technique were used to attempt to sequence an antibody. Dr. Anderson concludes that as of the late 1990's, it is doubtful that any scientist in the antibody field would have seriously considered attempting to determine the amino acid sequences of an antibody, much less have been routinely performing such a process at this time (*see* paragraph 5). The conventional manner of making a humanized antibody, by amplifying and sequencing cDNA encoding the antibody chains from a hybridoma, also could not have been performed without access to the hybridoma.

Finally, the Examiner alleges it would have been obvious to incorporate an antibody in an extended release composition for purposes of treatment. However, such an allegation changes the role of the 266 antibody from being an in vitro diagnostic to a therapeutic

antibody. Under MPEP 2141 quoted above such a change in function serves as evidence against obviousness.

For all of these reasons, it is respectfully submitted that the rejection should be withdrawn.

¶¶11-12. Claims 214 and 215 stand rejected on the basis that the phrase "two weekly" is unclear. Applicant has replaced with "once every two weeks."

¶13. Claims 56, 58, 61, 63-66, 71-76, 81-86, 92-94, 97, 164-183, 185-191, 194-199, 203, 205, 20-209 and 212-215 stand rejected as allegedly obvious over Findeis in view of Solomon and Becker. Findeis is alleged to teach administration of modulator compounds based on the amino acid sequence of a core aggregation domain of amino acid residues 17-20 or 17-21 of Aβ. Solomon is alleged to teach use of antibodies for inhibiting aggregation of Aβ, and a possible role of residues 12-17 of Aβ in aggregation. Becker is alleged to teach use of antibodies specific for beta amyloid predominantly in beta sheet conformation for treating Alzheimer's disease. The Examiner takes the view that it would have been obvious to replace a binding peptide of Findeis with a monoclonal antibody because it amounts to substituting one equivalent element with another to obtain predictable results.

The rejection is submitted to err from the use of impermissible hindsight in taking a selective view of the overall teachings of the art, ignoring or giving insufficient weight to evidence pointing away from the claimed invention, and not assessing predictability from the perspective of the skilled person at the relevant time. When viewing the art as a whole from the perspective of the skilled person at the relevant time, it is respectfully submitted that the skilled person would not have combined the references as proposed nor had a reasonable expectation of success that a humanized antibody as claimed would have had a therapeutic benefit.

The art as a whole did not point to the 17-20 or 21 region of Aβ as being the key region to focus therapeutic treatments. WO 95/08999 (cited by the IDS filed April 29, 2005 as cite no. 531) teaches away from the notion that residues 16-20 are an effective anti-aggregating epitope for targeting therapeutics. The '999 publication reports that peptides Lys Leu Val Phe

Phe (residues 16-20) and Lys Leu Val Phe Phe Ala Glu (residues 16-22) had no effect in a mouse model of Alzheimer's disease generated by co-injection of an aggregating peptide Aβ12-28, whereas certain other peptides had memory enhancing effects. This result would have suggested that Aβ16-20 and Aβ16-22 were ineffective at inhibiting aggregation of Aβ *in vivo*, and taught away from attempting to develop compounds binding to such epitopes to inhibit aggregation.

Becker also teaches away from using an antibody to a 17-20 or 21 epitope, at least implicitly. Becker proposes a theory whereby Aβ toxicity results from the beta-pleated sheet form of Aβ. Barrow, *J. Mol. Biol.*, 225(4):1075-1093 (1992) reported that residues 29-42 of Aβ are most associated with the β-sheet conformation (*see* Abstract paragraph 3 and p. 1088, second column, second paragraph) suggesting that one seeking to follow Becker's proposal would have selected an antibody directed to the 29-42 region.

Becker may also discuss antibodies having the opposite binding specificity (*i.e.*, binding to random coil without binding to beta-pleated sheet form). However, Becker does not unambiguously disclose an intent to administer such antibodies therapeutically or provide any reason to think they would be effective therapeutically. To the contrary, the thrust of the application is that there is a direct correlation between beta-sheeted structure and toxicity of Aβ and minimal toxicity is associated with samples of Aβ with a high degree of random coil structure, and that the beta sheet form be used to identify therapeutic compounds (col. 5, lines 26-41). In light of this proposed mechanism of action, an antibody binding to random coil Aβ without binding to beta sheet Aβ would have appeared to have the antithesis of the property Becker hypothesized might be useful for therapeutic use. The artisan would not thus simply assume that antibodies binding to the random coil form without binding to the beta pleated sheet form were intended to be used therapeutically.

Other art pointed to regions other than 17-20 or 21 of Aβ as having a role in aggregation or otherwise mediating toxicity. For example, Solomon reported an antibody termed AMY-33 inhibited Aβ aggregation in vitro. The antibody does not bind to an epitope within residues 13-28 as claimed (*see* Declaration of Dr. Seubert filed October 23, 2007). Another antibody used by Solomon raised to residue 8-17 of Aβ, which includes the region speculated by Solomon to contain ion binding sites, had only zero or slight effect. Elsewhere Solomon's group

has proposed that residues 1-9 of Aβ contribute mainly to solubility (Frenkel, *J. Neuroimmunol.* 95:136-142 (1999) at p. 140, col. 2, second paragraph, cited by the IDS filed August 16, 2002 as cite no. 245). Others have reported that the determinant role of Aβ aggregation is at the C-terminus (*see* Barrow, *J. Mol. Biol.*, 225(4):1075-1093 (1992), Abstract paragraph 3 and p. 1088, second column, second paragraph). Yankner et al., *Science* 250:279-282 (1990), (cited by the IDS filed June 24, 2008 as cite no. 917) has speculated that residues 25-35 of Aβ mediated toxic effects. To these can be added, Velazquez et al., *Nature Medicine* 3, 77-79 (1997), (cited by the IDS filed August 16, 2002 as cite no. 248) discussing residues 4-11 as being a potential target to inhibit interactions of Aβ with complement (at p. 77, paragraph bridging columns 1 and 2) and Giulian et al., *J. Neuroscience* 16, 6021-6037 (1996), (cited by the IDS filed July 30, 2004 as cite no. 470) reporting that both N-terminal and C-terminal regions of Aβ are required for toxicity (p. 6033, second column second paragraph). Although not all of these references negate Aβ17-20 or 17-21 as having a possible role in aggregation, they do teach away from it being the only such epitope or the critical epitope for therapeutic efficacy and set the artisan on a divergent path from the claimed methods. When the various reports in these references are viewed in the aggregate, a skilled person could not confidently have said which, if any, region of Aβ had particular significance for mediating aggregation or otherwise mediating toxicity, much less whether such a region had particular therapeutic significance.

The Examiner alleges that the combination of references simply represents a substitution of equivalent elements with predictable results. However, antibodies and small molecules are not equivalent, not least because antibodies are very large molecules, which might have been expected to have implications both for crossing the blood brain barrier and ability to penetrate amyloid deposits. Antibodies also differ in having effector functions, which although potentially useful against some pathogens, are also a source of inflammation, which would be of concern given the view that Alzheimer's disease was thought to be mediated at least in part by inflammation. Furthermore, neither small molecules nor antibodies had been demonstrated to have any activity against Alzheimer's disease. Given that treatment of Alzheimer's disease was regarded as being a difficult field in the 1990's as acknowledged by the Examiner and given the surprise of experts when disease modification was shown in an animal model by the present

application, it cannot be said that obtaining a successful treatment of Alzheimer's disease either using small molecules or antibodies was predictable. Selective reliance on Findeis over Becker for epitope specificity and vice versa for therapeutic strategy (*i.e.*, antibody versus small molecule) has the appearance of being guided by hindsight rather that what the skilled person would likely have inferred from the references at the relevant time.

A reasonable expectation of success is still required notwithstanding *KSR v. Teleflex,* 127 S.Ct 1727, 40-41, 82 U.S.P.Q.2d 1385, 95-96 (2007) because at the effective filing date of the claimed invention there were not a finite number of identified predictable solutions for treating Alzheimer's disease. None of the references does more than at best identifying a promising field in which to try to identify a suitable compound to treat Alzheimer's disease. The number of possible solutions is shown not only from the many epitopes within Aβ and molecule-types to interact with these epitopes (*e.g.*, antibodies, peptides, small molecules) discussed in the art but also by the fact that Aβ was but one of many avenues of investigation for treatment of Alzheimer's disease. Other areas included acetylcholine inhibitors, muscarinic agonists, tacrine, statins, NSAIDs, beta and gamma secretase inhibitors, and compounds directed against Tau (*see* Travis, *Science,* 309, 731-734 (2005) cited by the IDS filed July 19, 2007 as cite no. 857). The unpredictability of developing a therapeutic to Alzheimer's disease is shown by the strength and number of comments by independent experts expressing surprise on learning of the first demonstration of disease modification in an animal model as reported in the present application (*see* response of April 27, 2007). The challenging nature of the field is further evident from the "great unmet medical need" for an effective treatment (Travis, *Science,* 309, 731-734 (2005)).

Because the combination of references reflects impressible hindsight rather than the common sense approach of the artisan at the relevant time and does not provide a reasonable expectation of success, withdrawal of the rejection is respectfully requested.

¶14. Claims 5, 99 and 184 stand rejected as allegedlby obvious over Findeis in view of Solomon and Becker in further view of Schenk. Schenk is alleged to teach the 266 antibody. This rejection is traversed for the same reasons as described above.

In addition, the cited Schenk patent did not provide the sequences or reference a deposit of the 266 antibody. Applicant notes that the assignee of the Schenk patent, Elan Pharmaceuticals, Inc. provided samples of the 266 antibody to certain researchers subject to a materials transfer agreement limiting use of the antibody to research purposes and also provided a supply of the antibody to Innogenetics, who sold the antibody also with a restriction to research purposes. A declaration of Peter Seubert from related co-pending application, US Application No. 10/923,471 in this connection and an exemplary material transfer agreement are provided. Thus, the research community would not have access to the hybridoma and use of the antibody would be restricted to research purposes. Although the exact language used in restricting use of the antibody varied between agreements. , irrespective of the exact language, the restriction to research uses would not allowed commercial sale of a humanized antibody.

¶15. Claims 85 and 204 stand rejected as allegedly obvious over Findeis in view of Solomon and Becker in further view of Adair.

The interactions of human antibody constant regions with Fc receptors and complement can be useful against pathogens but can also contribute to undesired inflammation and autoimmunity (*see* Hogarth, *Current Opinion in Immunology* 2002, 14:798–802, submitted herewith; and, US 5,624,821 cited by the IDS filed July 19, 2007 as cite no. 718). The extent to which different isotypes interact with cells bearing Fc receptors and complement varies by isotype. Of the various human isotypes, IgG1, has been reported to be most effective in complement-mediated and cell-mediated cytotoxicity (*see* Clark at p. 6, cited by the IDS filed September 25, 2008 as cite no. 1091; and, paragraph 5 of the attached declaration of Shyra Gardai filed April 3, 2009 in co-pending application US Application No. 09/322,289). Such cyotoxicity may be a desirable attribute if the role of the antibody is to remove a parasite from the body. However, if the role of the antibody is to block a molecular interaction, for example, between a ligand and receptor, cytotoxicity is not needed and undesired because of the contribution to undesired inflammation. In treatment of Alzheimer's disease, it was not apparent that the role of an antibody, if any, was to remove Aβ. Without such knowledge and given the concern that Alzheimer's disease was mediated in part by inflammation, it would not have been

obvious to select the human IgG1 isotype because of concern this isotype would make the inflammation worse.

¶16. Claims 77-79 and 200-202 stand rejected as allegedly obvious over Findeis, in view of Solomon and Becker in further view of Pluckthun. Pluckthun is cited as teaching antibody fragments. Applicants traverse at least for the reasons already given in connection with Findeis, Solomon and Becker.

¶17. Claims 210, 211, 216 and 217 stand rejected as alleged obvious over Findeis in view of Solomon, Becker and Trang. Trang is alleged to teach measuring concentrations of a therapeutic antibody. Applicants traverse at least for the reasons already given in connection with Findeis, Solomon and Becker.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

Rosemarie L. Celli

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| In re application of: | Confirmation No. 8241 |
| SCHENK, Dale B. | Examiner: EMCH, GREGORY S. |
| Application No.: 10/923,471 | Technology Center/Art Unit: 1649 |
| Filed: August 20, 2004 | Declaration under 37 CFR 1.132 |
| For: PREVENTION AND TREATMENT OF AMYLOIDOGENIC DISEASE | |
| Customer No.: 20350 | |

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, John P. Anderson, state as follows:

1. I have a Ph.D. in Pharmacology. My current position is Senior Scientist at Elan Pharmaceuticals, Inc. I have been conducting research in biochemistry and molecular biology for over thirty years. I have used amino acid sequencing in my work on several occasions including the cloning and isolation of the beta-secretase enzyme as reported in *Nature* 402, 537-540 (1999). I am familiar with amino acid sequencing technology as it has evolved over the years, including in the late 1990's. A copy of my curriculum vitae is attached.

2. By the late 1990's, amino acid sequencing was primarily if not exclusively used for determining short peptide sequences. For example, one application was determining a partial peptide sequence, designing a probe or primer to encode that sequence and then using the primer as a means to select a gene or cDNA encoding the protein. This is how our group used amino acid sequencing in cloning the beta secretase enzyme. Another application was to characterize

the N-terminus of intact proteins; I used this to characterize processing of several beta secretase enzyme constructs I prepared. Although decades earlier amino acid sequencing had been used with heroic efforts to determine the full length sequences of a few proteins, such application had long since been discarded in favor of much more efficient and accurate DNA sequencing. By this approach, one would sequence the DNA and deduce the amino acid sequence from the DNA.

3. One of the difficulties of amino acid sequencing is that it is a cyclic process involving removing successive amino acids from a peptide. The removal process does not proceed to completion. Accordingly, successive cycles release amino acids of increasingly reduced purity increasing the likelihood of errors until eventually further determination of the sequence becomes impossible. The difficulties of amino acid sequencing are illustrated by the paper first reporting the amino acid sequence of Aβ (Glenner & Wong, *Biochem. Biophys. Res. Commun.* 122, 1131-35 (1984)). Although the peptide is about 40 amino acids long, the reported sequence contained only 24 amino acids and contained an error at position eleven compared with the now-known sequence of Aβ.

4. The difficulties in amino acid sequencing of an antibody are much greater than those in sequencing a simple peptide or determining a partial sequence of a protein. The heavy and light chains are each much longer than the length of sequence that can be read from a single sequence run. The chains would have to be separated from each other, and each chain must be cleaved into separate overlapping peptides, which would in turn have to be separated and individually sequenced. Separation of such a complex mixture was and remains technically difficult. Incomplete separation between the chains or peptides or both would result in cross-contamination, reducing the length of sequence that could be read from any peptide and

increasing the probability of error. Also, several of the amino acids in antibody chains are glycosylated, further complicating the analysis as the glycosylation interferes with detection of the modified amino acid and may interfere with the cleavage reactions. In addition, peptides must be immobilized for sequencing and glycosylation can interfere with this immobilization.

5. Because of all of these difficulties and errors associated with amino acid sequencing of an antibody, and because by the late 1990's, amino acid sequencing had all but been discarded as a technique for determining full-length sequences, it is doubtful that any scientist in the antibody field would have seriously considered attempting to determine the amino acid sequences of an antibody, much less have been routinely performing such a process at that time.

6. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

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# CURRICULUM VITAE

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**Education**

**BA**: Haverford College (1971-1975)
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**Ph.D.**: University of Wisconsin- Madison (1975-1982)
Major: Pharmacology

**Positions held:**

**Elan Pharmaceuticals, Inc. Department of Biology;** Senior Scientist 2005-present, Principal Scientist 2001-2005, Scientist 1992-2001; Research: Isolation and characterization of beta-secretase (BACE); characterization of pathology-associated modifications of α-synuclein

**Mount Sinai Medical Center, Department of Psychiatry and Fishberg Center for Neurobiology;** Assistant Professor 1990-1992, Research Associate 1987-1990; Research: Expression and modifications of the Alzheimer amyloid precursor protein (APP)

**Columbia University, Department of Anatomy and Cell Biology;** Associate Research Scientist 1985-1987; Research: Estrogen and insulin effects on neural development

**Yale University School of Medicine, Department of Pathology;** Postdoctoral Fellow (NRSA Fellowship)1982-1985, Principal Investigator: Jon s. Morrow, M.D., Ph.D.; Research: Interaction of erythrocyte spectrin with calmodulin, using photoactivatable crosslinking reagents, and with ATP, using fluorescence and HPLC binding assays

**University of Wisconsin-Madison, Department of Pharmacology;** Graduate Research Assistant 1975-1982, Advisor: Arnold E. Ruoho, Ph.D.; Research: Spectrin interaction with the erythrocyte membrane, using synthesized photoactivatable crosslinking reagents

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| In re application of: | Confirmation No. 8241 |
| SCHENK, Dale B. | Examiner: EMCH, GREGORY S. |
| Application No.: 10/923,471 | Technology Center/Art Unit: 1649 |
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| Customer No.: 20350 | |

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Peter Seubert, state as follows:

1. My current position is Vice President for Neurodegenerative Research at Elan Pharmaceuticals, Inc. (Elan).

2. Elan is in the business of conducting research and developing pharmaceuticals. In the course of this business, Elan's scientists often develop biological materials, such as antibodies. The mouse 266 antibody is an example of such antibody developed at Elan. Elan regards such biological materials as being its proprietary property for use by Elan and/or partners of Elan operating under a research agreement with Elan. It is not Elan's policy to freely distribute them to the scientific community.

3. From time to time Elan's scientists publish their work in scientific journals. Johnson-Wood et al., PNAS 94:1550-1555 (1997) and Seubert et al., Nature 359, 325-327 (1992) are examples of such publications.

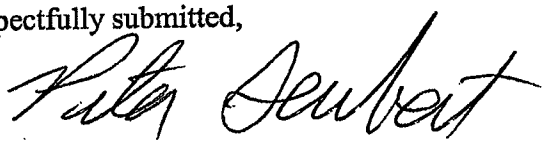
4. When biological materials, such as the 266 antibody are described in scientific journal articles, Elan sometimes receives requests from researchers at other institutions for samples of the materials. I am responsible for determining how to respond to such requests.

5. In responding to such requests, Elan's policy is to provide samples, if at all, only if the recipient will sign a material transfer agreement limiting use of the samples for research and prohibiting further transfer. Furthermore, for requests for samples of an antibody, such as the 266 antibody, Elan's policy is to provide only a sample of the antibody itself and not the hybridoma that produced the antibody.

6. Therefore, in responding to requests for the 266 antibody based on the antibody being mentioned in Johnson-Wood et al., PNAS 94:1550-1555 (1997) or Seubert et al. 359, 325-327 (1992) Nature 359, 325-327 (1992), Elan has not given anyone a sample of the hybridoma.

7. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,



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## MATERIAL TRANSFER AGREEMENT

REDACTED

### RECITALS

### TERMS AND CONDITIONS

The parties agree to the following terms and conditions for the disclosure, control and protection of the Information:

1. The period of disclosure of Information shall begin as of the date of this Agreement.

2. Upon the transmission and receipt of Information:

   (a) A confidential relationship with respect to such Information will immediately be established between Provider and Recipient;

   (b) Recipient will use all necessary care to prevent disclosure or release of Information to any third party, absent Provider's prior written authorization and consent; and

   (c) Recipient agrees that it will use the Information solely for the Purpose and not for the benefit of others except with prior written consent of an authorized representative of Provider.

3. All Information given or transmitted under the terms of this Agreement will continue to be Provider's proprietary and confidential information and will remain such, unless, as to any item of Information, such Information:

   (a) came lawfully into the possession of Recipient prior to the date of disclosure;

   (b) becomes public or available to the public other than through any act or default of Recipient amounting to breach of this Agreement;

(c) has been lawfully obtained by Recipient from a third party in lawful possession of such Information; or

(d) was independently developed by employees of Recipient who did not have access to or benefit from the Information.

4. Provider accepts no responsibility for any injury (including injury resulting in death), damage or loss from the use of MATERIALS.

5. Recipient assumes all responsibilities, liabilities and risks in connection with the receipt, handling, storage, and use of MATERIALS. Use of the MATERIALS will be in compliance with all applicable federal, state, and local laws and regulations.

6. Recipient understands that MATERIALS have not been approved for human use and agrees that the MATERIALS will not be administered to humans in any manner or form.

7. MATERIALS provided hereunder are experimental in nature, and are provided WITHOUT WARRANTY, EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION, WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE AND WITHOUT WARRANTY THAT THE USE OF THE MATERIALS WILL NOT INFRINGE ANY PATENT OR OTHER PROPRIETARY RIGHT OF A THIRD PARTY.

8. Recipient warrants that MATERIALS will be used only and solely for the Purpose specified in Exhibit A and will not be used by or through Recipient for any other purpose such as, for example, to support the development of any commercial product containing MATERIALS or discovered or derived from the use thereof, including use in screening assays. Any use of the MATERIALS by or through Recipient for any unauthorized purpose shall be deemed a material breach of this Agreement. In the event of such material breach, the results of the unauthorized research and any discoveries or inventions which arise therefrom (whether patentable or not) shall belong solely and exclusively to Provider, and Recipient shall take all reasonable and necessary actions to vest in Provider its ownership interest therein.

9. The results of the research performed with MATERIALS, underlying data and conclusions drawn from the study will not be disclosed by Recipient orally or by submission of a manuscript or abstract without Provider's express prior written consent. Recipient hereby grants Provider a worldwide, nonexclusive, fully paid-up license to use any improvement to, or invention arising from the use of, the MATERIALS ("Invention") for research and development purposes, including studies directed to the identification and development of a therapeutic. Recipient further hereby grants Provider a first option to negotiate an exclusive (or, at Recipient's option, nonexclusive) license under commercially reasonable terms to import, offer for sale, have sold and sell Inventions for commercial purposes.

10. MATERIALS are considered confidential and proprietary and are the sole property of Provider. Recipient will not attempt to ascertain or have ascertained the structure of the MATERIALS.

11. MATERIALS are not to be sold, transferred or otherwise distributed to any third party, or other investigator at Recipient not under Investigator's direct supervision, for any purpose without the prior written permission of Provider.

12. Any unused quantities of the MATERIALS will be disposed of according to prescribed federal, state and local guidelines or, at Provider's request, will be returned to Provider.

13. Recipient agrees to send Provider a copy of any proposed presentation or publication at least sixty (60) days prior to the date of the proposed submission, for review and written approval by Provider. Upon request, Recipient agrees to delay the submission of such publication for a further sixty (60) days to accommodate any patent filing or, at the option of Provider, to revise the abstract or publication to remove reference to any Information included in the proposed publication.

14. This Agreement shall expire on the date which is ten (10) years from the date shown above. Upon expiration of this Agreement, all written or tangible Information acquired by Recipient shall be returned to Provider, except that Recipient may retain one copy of the disclosed Information in its legal department files for the purpose of insuring compliance with its obligations herein.

15. This document contains the entire and complete Agreement between the parties with respect to the subject matter hereof, and supersedes all prior written or oral and any contemporaneous oral agreements. If any part of this Agreement is found by a court to be invalid or unenforceable, it shall be deemed modified to the extent necessary to allow enforcement, and all other portions of this Agreement not so modified shall remain in full force and effect. Any changes to this Agreement must be in writing and signed by both parties.

16. Recipient recognizes and agrees that nothing contained in this Agreement will be construed as granting any rights to Recipient, by license or otherwise, to Provider's Information except for the Purpose specified in this Agreement. Furthermore, the furnishing of MATERIALS under this Agreement shall not constitute any grant, option or license to Recipient under any patent or other rights now or hereafter held by Provider.

17. The parties recognize and agree that remedies at law for breach of this Agreement by Recipient will likely be inadequate and that Provider shall, in addition to any other rights to which it might have, be entitled to seek injunctive relief.

18. This Agreement shall be binding upon and inure to the benefit of the successors, assigns and legal representatives of the parties.

19. This Agreement shall be governed by and construed in accordance with the laws of the State of California, except for their conflict of laws principles. The parties agree to exclusive jurisdiction and venue of any actions or proceedings relating to this Agreement in the state and federal courts of San Francisco, California.

20. This Agreement may be executed in one or more counterparts, each of which shall be deemed an original but all of which together shall constitute one and the same document. This Agreement may be executed by facsimile. The parties agree that facsimile copies of signatures have the same effect as original signatures.

Effective as of the date shown above, and executed by:

**EXHIBIT A**

# MATERIAL TRANSFER AGREEMENT

ELN0004262 d

## AMENDMENT NUMBER ONE

THIS MATERIAL TRANSFER AGREEMENT AMENDMENT NUMBER ONE (the "Amendment") is effective as of December 1, 2007 (the "Amendment Effective Date") by and between Elan Pharmaceuticals, Inc., a Delaware corporation with a principal place of business at 800 Gateway Boulevard, South San Francisco, California 94080 ("Provider") and the University of Tokyo, a non-profit educational institution existing under the laws of Japan with an address of 7-3-1 Hongo Bunkyo-ku, Tokyo 113-0033, Japan ("Recipient").

## RECITALS

A. WHEREAS, Provider and Recipient have previously entered into a Material Transfer Agreement effective as of October 16, 2006 with an expiration date of October 15, 2016 (the "Agreement");

B. WHEREAS, Provider and Recipient mutually desire to amend the Agreement as set forth below;

NOW THEREFORE, Provider and Recipient agree as follows:

## TERMS AND CONDITIONS

1. The second sentence of Recital A of the Agreement shall be deleted in its entirety and replaced with the following:

> "Furthermore, Provider will be providing the following antibodies: 10D5 and 266 (hereinafter referred to as "MATERIALS") to the Recipient for use in research as described in Exhibit A (the "Purpose"). Provider will supply 46 mg of each of 10D5 and 266 antibodies; provided, however, that upon written request of Investigator, further shipments in excess of this amount, solely for the same Purpose, may be supplied at Provider's sole discretion."

2. Section 12 shall be amended and restated as follows:

> "Any shipments of MATERIALS in excess of the quantity specified above, if supplied, shall be subject to all of the terms and conditions of this Agreement. Any unused quantities of the MATERIALS will be disposed of according to prescribed federal, state and local guidelines or, at Provider's request, will be returned to Provider."

3. Except as modified herein, the Agreement remains in full force and effect and is hereby incorporated by this reference. Capitalized terms not otherwise defined herein shall have the meanings contained in the Agreement.

# Fc receptors are major mediators of antibody based inflammation in autoimmunity

P Mark Hogarth

There is now renewed interest in the role of antibodies in autoimmunity. Recent compelling evidence indicates that autoantibodies and the effector mechanisms they induce, for example, Fc receptor activation of leukocytes and/or the complement cascade, are central players in the development of autoimmunity, by perpetuating inflammation and perhaps even regulating the process itself. Of increasing interest are Fc receptors, which have been more closely investigated in the past decade using recombinant proteins, gene deficient mice and mouse models of human disease. These analyses point towards major roles of Fc receptors in antibody hypersensitivity reactions and by extension autoimmune disease, and they reveal opportunities in the development of novel therapeutic approaches in the treatment of autoimmune diseases.

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**Abbreviations**

| | |
|---|---|
| **FcR** | Fc receptor |
| **IL** | interleukin |
| **ITAM** | immunoreceptor tyrosine-based activation motif |
| **TNF** | tumour necrosis factor |

## Introduction

Antibodies are naturally potent inducers of inflammation. It is not surprising then that the identification of autoreactive antibodies in sites of inflammation has historically raised the question about such antibodies being primary mediators of the inflammation, or even central to the cause of the disease. Curiously, autoreactive antibodies have often been seen as secondary products of the disease process. Early clinical immunologists were able to show the presence of immune complexes or autoantibodies in inflamed tissues, such as the kidney in nephritis, the blood vessels in vasculitis and joints in rheumatoid arthritis. Certainly in some diseases antibodies have been clearly identified as the primary cause of morbidity, for example, in systemic lupus erythematosus (SLE) or immune thrombocytopenia purpura, whereas they have little if any role in others, for example, autoimmune Type I diabetes. However, and interestingly, in other more complex diseases such as rheumatoid arthritis, the role of antibodies has been dogged by controversy. Early studies showing the presence of abundant IgG-reactive rheumatoid factors in afflicted joints, together with the presence of large numbers of plasma cells, implicated antibodies as causal agents rather than as secondary consequences of changes in joint pathology induced by other factors.

Following the discovery of the T cell receptor, however, an enormous effort was devoted, largely unsuccessfully, to identifying T cells involved in the development of autoimmunity in patients. However, although there is general agreement that an initial loss of T cell tolerance generally promotes autoimmunity, in several autoimmune diseases it is likely that antibodies inflict tissue damage at sites distant from the T cell lesion. Thus, there is renewed interest in antibodies and in their effector systems in autoimmune processes.

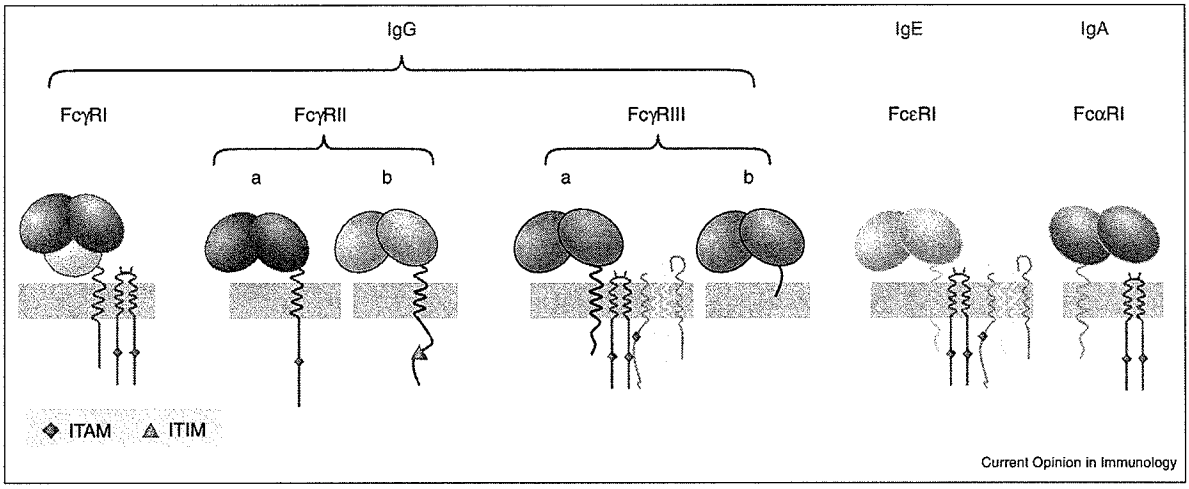
Indeed, as Fc receptors (FcRs) and/or the receptors of the complement cascade (C′ receptors) are the major effector systems induced by antibody, there has recently been an enormous effort to define their relative contributions to hypersensitivity reactions and ultimately to the disease processes. As a result, their roles in the regulation of immunity and autoimmunity are beginning to be understood.

In this brief review, I will focus largely on the recent interest in the role of Fc receptors in inflammation or in disease models and, where appropriate, refer to the complement system.

## Activating or inhibitory Fc receptors

Antibody activation of FcR-bearing cells *in vitro* and *in vivo* depends on the interactions of activating and inhibitory FcγR. The biochemistry of these interactions has been widely discussed in many recent reviews, which have detailed the structure and function of Fc receptors (Figure 1; [1,2]). In brief, the IgG receptor family consists of several activating receptors and a single inhibitory receptor. Of the activating receptors, only two are common to humans and mice (FcγRI, FcγRIIIa), both of which signal via their non-covalent association with a common low-molecular weight, dimeric FcR γ-chain that is also shared with the high affinity IgE receptor FcεRI and the IgA receptor FcαRI [1,2]. Specialised motifs (e.g. the immunoreceptor tyrosine-based activation motif, ITAM) in the tail of the FcR γ-chain signal cell-activating pathways via src family and syk tyrosine kinases [3]. Of particular interest, however, is that humans have two additional activating receptors: FcγRIIa and a lipid-anchored FcγRIIIb, which are not found in rodents and, until recently, had not been analysed in most animal models of autoimmunity or inflammation (Figure 1). These receptors also activate cells via src family kinases, but do so by unique processes. Notably, FcγRIIa is centrally placed in signalling processes in that FcγRIIIb and other Fc receptors may require FcγRIIa to initiate cell activation (see below). The inhibitory receptor FcγRIIb is common to human and mice and mediates its effect by the recruitment of tyrosine phosphatases via a specialised motif in its cytoplasmic tail (immunoreceptor tyrosine-based

**Figure 1**




Diagrammatic representation of human leukocyte FcRs. The tyrosines of the ITAM contained in the cytoplasmic tail are indicated as red squares; those of the ITIM as green triangles. Note also that up to three splice variants of the tail of FcγRIIb are known (FcγRIIb1, FcγRIIb2, FcγRIIb3).

inhibitory motif, ITIM) and cytoplasmic splice variants all contain this motif [2–4].

The mechanisms by which T and B lymphocytes are immunologically corrupted in the earlier phase of the induction of autoimmunity are dealt with elsewhere in this volume and are extensively reviewed in the literature, but there are two points that I would make on the role of complement and Fc receptors in this process. First, in both cases they have significant roles in the regulation of immune processes; FcR are involved in the maintenance of B cell unresponsiveness and B cell tolerance via the specialised inhibitory Fc receptor for IgG — FcγRIIb [4,5], and there is speculation on a role for complement in aspects of tolerance induction [6•]. Thus, disruption of these systems may lead to autoimmunity. Second, the uptake of antigen once complexed with immunoglobulins is a key process during the development of an immune response. Fc receptors and C′ receptors have been shown to participate in this process, but of particular importance is the high affinity IgG receptor, FcγRI [7•,8]. This receptor has a 10–100-fold higher affinity for IgG compared to the low affinity IgG receptors FcγRII and FcγRIII. Thus, FcγRI acts early in the immune response, capturing immune complexes at low antibody concentrations for internalisation, reprocessing and subsequent presentation of the antigen — such processes occur long before engagement of other low-affinity Fc receptors [7•,8–10]. This at least seems to be the case in mice where in the absence of FcγRI immune responses are impaired and antigen capture in immune complexes by macrophages is profoundly reduced [7•]. Thus, these data raise the possibility that autoimmunity may be enhanced by autoantigen–antibody complex uptake early in autoimmune responses. Third, FcR binding of immune complexes can drive the differentiation of dendritic cells towards more mature and highly efficient antigen presenting cells (APCs; [9]).

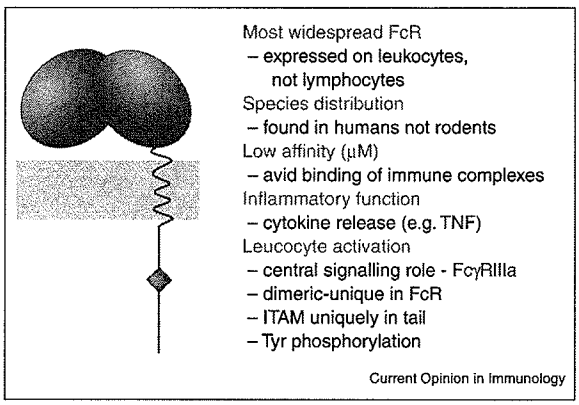
Collectively then both immunoglobulin Fc receptors and the complement system (and its receptors) have key roles in developing and driving immunity, and possibly autoimmune responses.

## Fc receptors and inflammation

The work of the early immunologists during the 1950s and 1960s defining antibody hypersensitivity reactions concluded that the antibody-induced destruction in Type III hypersensitivity (e.g. serum sickness, Arthus reaction) was largely dependant on complement. Interestingly, however, after experimental depletion of complement a robust inflammatory response was still observable, implying complement-independent mechanisms also existed — FcRs had not been defined at that stage. Since those early days, the mechanisms of IgG damage in pathological or autoimmunity have been continually attributed largely to complement activation, but the past ten years in particular has seen the rise in acceptance of Fc receptors as a major, perhaps primary, effector of antibody-based inflammation [11].

The first direct demonstration of a possible primary role of Fc receptors in antibody-induced inflammation was made almost a decade ago by experiments using soluble recombinant forms of the ectodomains of human FcγRIIa in rats as a competitive inhibitor of Fc receptor function [11]. This soluble FcR completely inhibited Type III hypersensitivity reactions (the Arthus reaction) indicating that Fc receptors can be a principal driver of this type of inflammation. This conclusion was subsequently confirmed by

**Figure 2**




FcγRIIa and its characteristics. The receptor is composed of two extracellular domains which are highly related to FcgRIIb but has unique transmembrane and intracellular regions. The two phosphorylatable tyrosines are found in the signaling ITAM represented by the diamond.

the use of Fc receptor-deficient animals; mice lacking the activating type FcγRIII (or lacking the common FcRγ-chain — resulting in impaired expression of, and signalling by, FcγRI and FcγRIII) show profoundly reduced inflammation, and mice lacking FcγRI also show some reduced inflammation [2,7•,8,12]. Similarly, Type II reactions involving cytotoxic antibodies are profoundly affected by inactivation of activating FcR. Further evidence for the role of FcR in inflammation is apparent when the inhibitory FcγRIIb is deleted, resulting in exaggerated antibody responses, hypersensitivity reactions or clinically obvious autoimmunity [13–16].

These data suggest that the balance between activating FcR and inhibitory FcγRIIb is critical in the regulation of inflammatory responses by both control of antibody responses and inflammatory leukocyte activation. It is also interesting to note that autoimmune-prone mice show genetic defects in the promoter of the mouse FcγRIIb gene [17].

## Animal models, human disease and the unique FcγRIIa

It is also clear from the study of disease models in animals [18] and genetic studies in mice and humans that FcRs are risk factors for autoimmune disease [17,19–22]. This is further supported by studies of autoimmunity *in vivo* in mice lacking FcR; such studies generally conclude that inactivation of the inhibitory FcγRIIb exacerbates existing autoimmunity and predisposes to spontaneous disease [5,13,14,16,23], whereas inactivation of the activating receptors ablates or ameliorates tissue destruction in models of autoimmune disease [7•,8,24,25]. The opposing effects of inactivation of the activating or inhibitory FcR argue strongly for a central role of FcR in the regulation of autoimmunity and initiation of local inflammation.

One of the striking deficiencies of the extensive analyses described above and in the study of Fc receptors in human disease is the lack of models for studying the uniquely human FcγRIIa (Figure 2). This Fc receptor has several features that are unique: first, it is not found in mice or any other mammal other than humans. Second, it is the only Fc receptor, and indeed one of the few immunoreceptors, where the ITAMs occur in the ligand IgG binding chain. Typically these motifs are required for the activation signalling pathways and are always contained in low molecular weight dimers that are noncovalently associated with the ligand-binding chain, for example, the common FcR γ-chain, Igα and Igβ of the B cell receptor, and the T cell receptor-associated CD3 molecules [1–3]. Third, FcγRIIa forms a noncovalent homodimer, another unique feature among immunoreceptors generally and FcR specifically. The dimer juxtaposes the cytoplasmic tails of each monomer in a configuration that resembles the covalent FcRγ–chain homodimer [26]. Fourth, signalling by several other FcγR is dependant on FcγRIIa; the lipid-anchored neutrophil specific FcγRIIIb is dependant on FcγRIIa [27], and recent data indicates that in mature macrophages FcγRI functionally associates with, and signals through, FcγRIIa (J Allen, personal communication). Therefore, FcR signalling, at least in some cases, is 'focused' through FcγRIIa.

Although the studies using recombinant receptors and gene knockout mice have been highly informative, none have examined the impact of this unique receptor in autoimmunity or hypersensitivity reactions. Such analyses are especially important as, apart from its unique characteristics, it is the most widespread of all the Fc receptors — present on platelets and every leukocyte except T and B-lymphocytes and some natural killer (NK) cells [1]. It is of interest then to note that FcγRIIa transgenic animals have only recently become available and, in models of immune thrombocytopenia, they match the human clinical picture [28,29]. Most importantly, however, our unpublished studies (C Tan, P Mottram, PM Hogarth, unpublished data) show that these mice are profoundly sensitive to antibody-induced inflammation, including the Arthus reaction and adoptive transfer of erosive arthritis with antibodies from the KRN/non-obese diabetic (NOD) transgenic mice (see below). The KRN mice are transgenic for a T cell receptor that, when crossed to NOD mice, develops and antibody dependant joint specific autoimmune disease with the features of rheumatoid arthritis. The presence of the FcγRIIa converts genetically resistant mice to susceptible in collagen-induced arthritis, a model where antibody has traditionally been thought to be of relatively minor importance.

Most interestingly the FcγRIIa transgenic mice also develop a spontaneous autoimmune syndrome with features similar to rheumatoid arthritis (i.e. erosive pannus-forming arthritis), systemic lupus erythematosus (i.e. glomerulonephritis with immune complex deposition in kidneys), pneumonitis and a non-erosive arthritis. Taken together these data imply that, even in the

presence of endogenous FcR, FcγRIIa is the major activator of inflammation.

It would be wrong, however, to conclude that FcRs are always the only factor involved, and it is clear that FcR-independent mechanisms of destructive antibody-based inflammation are evident in models of autoimmunity. One interesting recent model is described in a series of papers from Mathis and colleagues [30–33]. The KRN TCR transgenic mice crossed to NOD mice develop an erosive arthritis and make antibodies against the cytoplasmic enzyme glucose-6-phosphate isomerase, which are sufficient to transfer disease. This is dependant on both C′ signalling through the alternative pathway and also on FcR [30–33].

Thus, it appears likely that the role of complement and FcR receptors are likely to be interrelated as indeed has been suggested in a model of vitiligo [34].

## Therapeutic approaches to autoimmune disease

FcRs have emerged as an attractive therapeutic target, as they act early in inflammation and their engagement by immune complexes is a potent signal for the release of mediators such as tumour necrosis factor (TNF) or interleukin (IL)-1 [35–37]. Thus, strategies to prevent Fc receptor activation are potentially attractive especially as they would act upstream of current strategies that neutralise mediators when they are released [38••]. In rheumatoid arthritis it is clear that one of the principal mediators is TNF [38••]. This has been validated by the use of anti-TNF antibodies with impressive clinical effects [38••]. Likewise, the IL-1 receptor antagonist protein now clinically available can also ameliorate inflammation associated with rheumatoid arthritis. Soluble recombinant receptors are also a therapeutic possibility with an antagonising immune complex and an antagonising FcR function — and as are a variety of other recombinant proteins [11]. Likewise, the well-documented role of complement in inflammation also means that inhibiting the complement cascade (or its receptors) may be useful therapeutically [39].

## Conclusions

With advances in structural biology and the recent solution of the three dimensional structure of FcγRIIa [26,40] and other FcγRs [41,42], the design of small chemical entities to inhibit receptor function is now a possibility [43]. Furthermore, given a possible central role of FcγRIIa in FcR signalling, this receptor may be an appropriate target for novel therapies. The possible advantages of FcR-based therapeutics over the current mediator-neutralising treatments, such as anti-TNF antibodies or IL-1 receptor antagonist protein, are that these entities could act earlier in the inflammatory cascade. Whether this will ultimately be the case remains to be determined, but the combination of animal and human studies with advances in structural genomics, medicinal chemistry and a broader understanding of immunological processes now makes FcR antagonism a real possibility.

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- • of special interest
- •• of outstanding interest


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TOWNSEND and TOWNSEND and CREW LLP

By:_____

PATENT
Attorney Docket No.: 15270J-004740US

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of:

Schenk, Dale B.

Application No.: 09/322,289

Filed: May 28, 1999

For: PREVENTION AND TREATMENT OF AMYLOIDOGENIC DISEASE

Customer No.: 20350

Confirmation No. 7773

Examiner: Kolker, Daniel E.

Technology Center/Art Unit: 1649

DECLARATION OF SHYRA J. GARDAI UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
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Sir:

I, Shyra J. Gardai state, as follows:

1. My current position is a scientist at Elan Pharmaceuticals, Inc (Elan). I understand the above application is assigned to Elan or one of its affiliated companies.

2. I have a B.S. in biochemistry/microbiology from the University of Idaho (1997), and a Ph.D. in Innate Immunology from the University of Colorado Health Sciences Center (2002). A list of my publications is attached. One of my responsibilities at Elan has been to perform experiments comparing antibodies having different isotypes. In the course of my studies and subsequently as a scientist, I have read many texts of immunology, read the scientific literature, particularly that relating to my own work, and have attended and presented at conferences relating to my work.

3. I understand that the Examiner of the above application is taking the view that there is a general rule well known to those in the field that an antibody having a human IgG1 isotype binds more strongly to an antigen than an otherwise identical antibody having another human IgG isotype. However, I have no recollection of having heard of such a general proposition before. Based on my experience and knowledge of the scientific literature, there are some instances where one human IgG isotype may bind more strongly than other isotypes, but these are dependent on a particular antibody or antigen. I have reviewed WO 91/16928, which I understand the Examiner is citing as a basis for his position. I read this reference as reporting an example in which a particular antibody has higher avidity in the human IgG1 isoform but not as establishing a general rule. I am aware of another reference McClosekey et al., Immunology 88, 169-173 (1996) reporting the order of dissociation rate constants for human isotypes as being IgG4 less than IgG3 less than IgG2 less than IgG1 Because the on-rate constants for the different isotypes were similar (see Table 1), a lower dissociation rate constant translates into a higher binding strength (i.e., human IgG4 has the highest binding strength and human IgG1 the weakest binding strength). To reiterate, however, both McClosekey and WO 91/16927 are just examples, and I have not heard of a general rule that antibodies with human IgG1 isotype (or human IgG4) bind more strongly than other human IgG isotypes irrespective of a particular antibody or antigen. I believe based on my knowledge and experience, such a rule would not be accurate.

4. In selecting a human isotype for a humanized antibody, I would be most interested in the functional properties of the different isotypes and their relevance to the proposed mechanism of the antibody. I would not assume a priori there was any meaningful difference in affinity between different human IgG isotypes, and unless a substantial difference in binding strength was demonstrated experimentally for a particular antibody, possible variations in binding

strength would not be a significant factor in selecting a human IgG isotype. If a significant difference in binding strength between isotypes was demonstrated for a particular antibody, it would still not be determinative for isotype selection, but I would take affinity into account together with other functional properties in selecting an isotype.

5. Different nomenclature is used for human and mouse IgG isotypes. The human isotypes are referred to as IgG1, IgG2, IgG3 and IgG4. The mouse isotypes are referred to as IgG1, IgG2a, IgG2b and IgG3. The different isotypes differ in a number of functional properties including complement activation, Fc gamma receptor binding, and mast cell binding. Although there is no single human isotype having identical functional properties to a mouse isotype, there is a similarity between particular human isotypes and corresponding mouse isotypes. The isotype correspondence between human and mouse isotypes does not follow simply from their respective names. For example, human IgG1 is not the closest human equivalent of mouse IgG1. The human IgG1 isotype has the properties of strongly interacting with complement and Fc gamma receptors. The most similar mouse isotype is mouse Ig2A. Mouse IgG1 interacts substantially less well with complement and Fcgamma receptors. The most similar human isotypes are IgG2 and IgG4. Mouse IgG1 also shares the property of human IgG4 of binding to mast cells. If I were selecting an isotype for a humanized version of a mouse IgG1 antibody and wanted the human isotype to perform most similarly to the mouse antibody, I would therefore select a human IgG2 or IgG4 isotype.

6. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States

Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Shyra J. Gardai

Date: 3/2/09

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Publication list

1: Surfactant proteins A and D suppress alveolar macrophage phagocytosis via interaction with SIRP alpha. Janssen WJ, McPhillips KA, Dickinson MG, Linderman DJ, Morimoto K, Xiao YQ, Oldham KM, Vandivier RW, Henson PM, Gardai SJ. Am J Respir Crit Care Med. 2008 Jul 15;178(2):158-67. Epub 2008 Apr 17.

2: Apoptotic cells, through transforming growth factor-beta, coordinately induce anti-inflammatory and suppress pro-inflammatory eicosanoid and NO synthesis in murine macrophages. Freire-de-Lima CG, Xiao YQ, Gardai SJ, Bratton DL, Schiemann WP, Henson PM. J Biol Chem. 2006 Dec 15;281(50):38376-84. Epub 2006 Oct 20.

3: ATP-binding cassette transporter A7 enhances phagocytosis of apoptotic cells and associated ERK signaling in macrophages. Jehle AW, Gardai SJ, Li S, Linsel-Nitschke P, Morimoto K, Janssen WJ, Vandivier RW, Wang N, Greenberg S, Dale BM, Qin C, Henson PM, Tall AR. J Cell Biol. 2006 Aug 14;174(4):547-56.

4: Recognition ligands on apoptotic cells: a perspective. Gardai SJ, Bratton DL, Ogden CA, Henson PM. J Leukoc Biol. 2006 May;79(5):896-903. Review.

5: Cell-surface calreticulin initiates clearance of viable or apoptotic cells through trans-activation of LRP on the phagocyte. Gardai SJ, McPhillips KA, Frasch SC, Janssen WJ, Starefeldt A, Murphy-Ullrich JE, Bratton DL, Oldenborg PA, Michalak M, Henson PM.
Cell. 2005 Oct 21;123(2):321-34.

6: Oxidants inhibit ERK/MAPK and prevent its ability to delay neutrophil apoptosis downstream of mitochondrial changes and at the level of XIAP. Gardai SJ, Whitlock BB, Xiao YQ, Bratton DB, Henson PM. J Biol Chem. 2004 Oct 22;279(43):44695-703. Epub 2004 Jul 30.

7: Phosphorylation of Bax Ser184 by Akt regulates its activity and apoptosis in neutrophils. Gardai SJ, Hildeman DA, Frankel SK, Whitlock BB, Frasch SC, Borregaard N, Marrack P, Bratton DL, Henson PM. J Biol Chem. 2004 May 14;279(20):21085-95. Epub 2004 Feb 6.

8: By binding SIRPalpha or calreticulin/CD91, lung collectins act as dual function surveillance molecules to suppress or enhance inflammation. Gardai SJ, Xiao YQ, Dickinson M, Nick JA, Voelker DR, Greene KE, Henson PM. Cell. 2003 Oct 3;115(1):13-23.

9: Peroxisome proliferator-activated receptor gamma (PPARgamma) expression is decreased in pulmonary hypertension and affects endothelial cell growth. Ameshima S, Golpon H, Cool CD, Chan D, Vandivier RW, Gardai SJ, Wick M, Nemenoff RA, Geraci MW, Voelkel NF. Circ Res. 2003 May 30;92(10):1162-9. Epub 2003 Apr 24.

10: Oxidant-mediated mitochondrial injury in eosinophil apoptosis: enhancement by glucocorticoids and inhibition by granulocyte-macrophage colony-stimulating factor. Gardai SJ, Hoontrakoon R, Goddard CD, Day BJ, Chang LY, Henson PM, Bratton DL. J Immunol. 2003 Jan 1;170(1):556-66.

11: Interleukin-15 inhibits spontaneous apoptosis in human eosinophils via autocrine production of granulocyte macrophage-colony stimulating factor and nuclear factor-kappaB activation. Hoontrakoon R, Chu HW, Gardai SJ, Wenzel SE, McDonald P, Fadok VA, Henson PM, Bratton DL. Am J Respir Cell Mol Biol. 2002 Apr;26(4):404-12.